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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,478	04/20/2001	James W. Schumm	016026-9238	4278

23510 7590 07/03/2002

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/03/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,478	SCHUMM ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

1. Claims 21-55 are objected to because the claim contains more than one period. For example, SEQ ID NO. 1 contains a period and the end of the claim contains a period. As provided in the MPEP 2422:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

This objection may be overcome by amending SEQ ID NO. 1 to read SEQ ID NO: 1 (see MPEP 608.01(m)).

Additionally the claims contain periods following the steps "a.". This objection may be easily overcome by amending the claims such that the steps are denoted by (a) instead of "a.".

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 28 is indefinite over the recitation "in step (e)" because Claim 21, from which Claim 28 depends does not contain a step (e). It appears as though applicant

may have intended to require step (d). Thus, as written, the claims are unclear what step (e) requires.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

3. Claims 21, 26-34, 39, 48-51, 53-55 are rejected under 35 U.S.C. 102(e) as being anticipated by Schumm et al. (5,783,406, July 1998).

In one embodiment, the instant claims are drawn to methods of simultaneously determining at least two makers selected from HUMCSF1PO and HUMTH01.

Schumm et al. (herein referred to as Schumm-1) teaches methods of simultaneously determining the alleles present in at least two STR loci from DNA samples wherein the loci are HUMCSF1PO, HUMFESFPS and HUMTH01 (limitations of Claim 21, 26, 48, 51). Schumm-1 teaches numerous primers which allow

amplification in multiplex systems. For example the primers for the loci HUMTH01 of 5,783,406, namely SEQ ID NO: 21 and 22, are identical to SEQ ID NO: 27 and 28 of the instant application (limitations of Claim 27, 50). Schumm-1 teaches and describes the method of separation and detection of the multiple alleles using separation by denaturing polyacrylamide gel electrophoresis and comparison to allelic ladder using silver staining or fluorescence detection (col 9; col 11-12)(limitations of Claims 28-31, 53-54). Schumm-1 teaches that amplified separately loci but display allele size ranges which do not overlap one another (limitations of Claim 32, 49). Schumm-1 teaches extracting DNA from blood samples, hair, semen, placental cells, fetal cells (col 10)(Claim 33). Schumm-1 teaches kits that utilize the process described (col 12)(limitations of Claims 34, 39, 55). Therefore, since Schumm-1 teaches every limitation of the claimed invention, Schumm anticipates the claims.

4. Claims 21, 26-34, 39, 48-51, 53-55 are rejected under 35 U.S.C. 102(e) as being anticipated by Schumm et al. (5,674,686, October 1997).

In one embodiment, the instant claims are drawn to methods of simultaneously determining at least two makers selected from HUMCSF1PO and HUMTH01.

Schumm et al. (herein referred to as Schumm-2) teaches methods of simultaneously determining the alleles present in at least two STR loci from DNA samples wherein the loci are HUMCSF1PO, HUMFESFPS and HUMTH01 (limitations of Claim 21, 26, 48, 51). Schumm-2 teaches numerous primers which allow amplification in multiplex systems. For example the primers for the loci HUMTH01 of

5,783,406, namely SEQ ID NO: 21 and 22, are identical to SEQ ID NO: 27 and 28 of the instant application (limitations of Claim 27, 50). Schumm-2 teaches and describes the method of separation and detection of the multiple alleles using separation by denaturing polyacrylamide gel electrophoresis and comparison to allelic ladder using silver staining or fluorescence detection (col 9; col 11-12)(limitations of Claims 28-31, 53-54). Schumm-2 teaches that amplified separately loci but display allele size ranges which do not overlap one another (limitations of Claim 32, 49). Schumm-2 teaches extracting DNA from blood samples, hair, semen, placental cells, fetal cells (col 10)(Claim 33). Schumm-2 teaches kits that utilize the process described (col 12)(limitations of Claims 34, 39, 55). Therefore, since Schumm-2 teaches every limitation of the claimed invention, Schumm anticipates the claims.

5. Claims 21, 23, 26, 29-31, 48 are rejected under 35 U.S.C. 102(a) as being anticipated by Schumm et al. (Fourth International Symposium on Human Identification, 1993).

Schumm et al. (herein referred to as Schumm-3) teaches a method for the rapid and easy interpretation of DNA STR markers. Schumm-3 provides a gel which is a fluorescein-labeled multiplex of the loci CSF1PO, TPOX, TH01 and vWF (page 180, col 1). Schumm-3 also teaches that the loci can be detected using silver staining (page 180, col 1). Therefore, Schumm-3 teaches a method of simultaneously determining the alleles present at atleast two loci, for example HUMTH01 and HUMCSF1PO; HUMTH01

and HUMTPOX; HUMCSF1PO and HUMTPOX. Therefore, Schumm-3 teaches each limitation of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 21, 26-27, 29-31, 33, 48-55 are rejected 35 U.S.C. 103(a) as being unpatentable over Fregeau et al. (BioTechniques, 1993).

Fregeau teaches DNA typing with fluorescently tagged STRs for a sensitive and accurate approach to human identification. Fregeau teaches a multiplex system which contains HUMCD4, HUMFABP, and HUMCATBP2 (pg. 114, col. 3). DNA for the

multiplex amplification reaction was extracted from blood, hair roots, dried bloodstains (pg. 101, col. 3, para. 1)(limitations of Claim 33). Fregeau demonstrates that primers for STR systems HUMHPRT, HUMTH01, HUARA, HUMCD4, HUMFABP, HUMPLA2A1 and HUMRENA4 were used to amplify genomic DNA (pg. 102, col. 1, and Table 1). Fregeau teaches primers identical to the primers of SEQ ID NO: 1, 2, 9, 15, 16, 19, 20, 27, 28, and 30 (Table 1)(limitations of Claim 27). Fregeau teaches HUMVWF, HumFABP, HumACTBP2 and D21S11 all have the same annealing temperature of 64 to 65 degrees and have been shown to permit multiplex amplification which saves in reagents and sample template (pg. 117, col. 3, para 2). Further, HumCD4, HumARA, HumTH01 have the same optimal annealing temperature, 68 degrees. The STR alleles were then separated and detected on a denaturing polyacrlamide gel electrophoresis (pg. 106)(limitations of Claim 29). The fluorescent amplification products were resolved on polyacrylamide gels with various gel parameters varied (pg. 103, col. 1)(limitations of Claim 31). A comparison was made between allele sized from silver-stained polyacrylamide gels and automated fluorescent analysis (pg. 110, col. 3)(limitations of Claim 30). A four STR system, HUMCD4, HUMHPRT, HUMTH01, HumARA, was explored using additional amplification cycles. Fregeau describes multiplex amplification of polymorphic STR sequences of loci including HUMHPRTB, HUMTH01, HUMCD4, HUMFABP and HUMPLA2A (pg. 117, col. 3, para. 2)(limitations of Claim 26). Empirical evaluation, a specific annealing temperature for each of the STR systems was found to generate consistent allelic profiles with high specificity and sensitivity after 28 cycles of amplification (pg. 115, col. 1). Several benefits of STRs analysis was

elucidated including the need for only minimal amounts of template DNA, the ability to resolve STR alleles on sequencing gels using radiolabeled primers or having been processed with cold primers and detected after silver staining, and the amenability of STRs to automation (pg. 100-101)(limitations of Claim 30). Further, Fregeau teaches that careful selection of a refined polyacrylamide gel system and appropriate STR loci that have allele size ranges that are mutually resolvable should allow for additional systems to be analyzed with the same fluorescent tag (pg. 117, col. 3).

Fregeau does not specifically perform the multiplex reaction with the specifically recited combinations of STR loci.

However, Fregeau sets forth all of the conditions for simultaneously determining the alleles present in at least two STR loci by multiplex of at least two STR loci as discussed above.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to have performed the experiment taught by Fregeau to have obtained the claimed invention. The skilled artisan would have been motivated to combine the loci taught by Fregeau to make additional combinations of loci suitable for identifying alleles simultaneously because Fregeau teaches all of the conditions necessary for the multiplex co-amplification assay and provides a reasonable expectation for success by showing multiplex amplification of a number of different STRs using the guidelines taught in the reference. For example, Fregeau teaches that HUMTH01 and HUMCD4 both have annealing temperatures of 68 degrees, and have different allele size (bp) which do not overlap (Table 1 and Table 3). Also, Fregeau

teaches that ACTBP2 and HUMFABP both have annealing temperatures of 64 degrees and do not have overlapping allele sizes (Table 1 and Table 3). Therefore the at least two STR loci would contain clearly distinguishable STR allelic profiles (pg. 115, col. 3) and it would have been obvious to combine these two STR loci to obtain the claimed invention. The ordinary artisan would have had a reasonable expectation of success for co-amplfiying the HUMTH01 and HUMCD4 loci, for example, in the same tube because the primers which amplify these loci had the same optimal annealing temperature. The ordinary artisan would have been motivated to have co-amplified these loci, as opposed to pooling the amplified products, because Fregeau teaches that the multiplex coamplficiation approach requires less template DNA per analysis which is a definite advantage where there is limited sample (page 101, col 2). The routine tweeking of the multiplex system is not considered undue experimentation. As admitted in the specification, "successful combinations are generated by trial and error (routine experimentation) of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified"(pg. 10, lines 10-13). Thus, varying certain parameters to meet the specific needs of the STR system is routine experimentation. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the STR combination selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results

should be considered unexpected in any way as compared to the closest prior art. Therefore, the combinations of the instant application would have been obvious over Fregeau.

1. Claims 21-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caskey (US. Pat 5,364,759) and Kimpton (Int. J. Leg. Med, 1994) in view of Kimpton (PCR Methods and Applications, 1993) or Fregeau (BioTechniques, 1993) or Urquhart (Int. J. Leg. Med, August 1994).

Caskey discloses the claimed method that includes obtaining a DNA sample, amplifying STR sequences from the DNA sample, and evaluating the amplification products for identification (col. 7, lines 4-10). Caskey teaches a definition of "multiplex polymerase chain reaction (mPCR)"(col. 6, lines 34-68). Further, Caskey teaches that mPCR includes a) primers composed of similar GC base compositions and lengths, b) longer extensions times up to 8 fold the normally utilized times and c) minimization of the number of PCR cycles performed to achieve detection. Caskey teaches that mPCR reaction is optimized for each reaction (col. 6, lines 65-66). Caskey identifies STR loci by searching all human sequences in GenBank (Example 1, col. 8). Strategies to determine the sequences flanking STRs are disclosed in Example 3 (col. 10). Although Caskey teaches that in a reaction with HUMARA and HUMFABP alleles appear as widely spaced doublets such that adjacent alleles overlap, different label may be applied to the different loci to unambiguously identify the alleles (col. 18). Caskey teaches the primers of SEQ ID NO: 15, 16, 19, 20, 27, and 28 as primers for the

amplification of HUMFABP, HUMPRTB, and HUMTH01, respectively. As described in Example 7, the comparison of amplified alleles by polyacrylamide gel electrophoresis and visualization of the DNA by fluorescent analysis. STR markers can be detected with non-denaturing and denaturing electrophoretic systems (limitations of Claim 29). Silver staining detection methods are all applicable (limitations of Claim 30). Additionally, the loci are selected so that the amplification products of the alleles from different loci do not over lap (limitations of Claim 32). Further, Caskey teaches that the source of DNA to be tested can be any medial or forensic sample and can include blood, semen, vaginal swabs, tissue, hair, saliva, urine and mixtures of body fluids (col. 6, para. 2)(limitations of Claim 33). Caskey discloses the use of allelic ladders as internal standards (col. 7, lines 15-19, and col. 19, lines 15-18)(limitations of Claim 28). Additionally, Caskey teaches kits which contains a container having oligonucleotide primer pair for amplifying STRs and optionally, standards (col. 8 and col. 21, Example 10)(limitations of Claim 34-39, 55).

Kimpton (Int. J. Leg. Med) teaches a multiplex amplification of four tetrameric STR loci. Kimpton (Int. J. Leg. Med) further teaches adjustment of most of the conditions of the multiplex system to optimize results (pg. 303-309). For example, Kimpton (Int. J. Leg. Med) teaches buffer concentration, primer concentration, deoxynucleotide triphosphate concentration, Taq polymerase concentration, template DNA concentration, number of amplification cycles, denaturing temperature, effect of annealing temperature, ionic strength and pH, and gel type variation to optimize the multiplex system.

Neither Caskey nor Kimpton specifically teach the combinations of loci recited in the instant claims.

However, Fregeau teaches DNA typing with fluorescently tagged STRs for a sensitive and accurate approach to human identification. Fregeau teaches a multiplex system which contains HUMCD4, HUMFABP, and HUMCATBP2 (pg. 114, col. 3)(limitations of Claim 21, 48-54). DNA for the multiplex was extracted from blood, hair roots, dried bloodstains (pg. 101, col. 3, para. 1)(limitations of Claim 33). Fregeau demonstrates that primers for STR systems HUMHPRT, HUMTH01, HUARA, HUMCD4, HUMFABP, HUMPLA2A1 and HUMRENA4 were used to amplify genomic DNA (pg. 102, col. 1, and Table 1). Fregeau teaches primers identical to the primers of SEQ ID NO: 1, 2, 9, 15, 16, 19, 20, 27, 28, and 30 (Table 1)(limitations of Claim 27). Fregeau teaches HUMvWF, HumFABP, HumACTBP2 and D21S11 all have the same annealing temperature of 64 to 65 degrees and have shown to permit multiplex amplification which saves in reagents and sample template (pg. 117, col. 3, para 2). Further, HumCD4, HumARA, HumTHO01 have the same optimal annealing temperature, 68 degrees. The STR alleles were then separated and detected on a denaturing polyacrlamide gel electrophoresis (pg. 106)(limitations of Claim 29). The fluorescent amplification products were resolved on polyacrylamide gels with various gel parameters varied (pg. 103, col. 1)(limitations of Claim 31). A comparison was made between allele sized from silver-stained polyacrylamide gels and automated fluorescent analysis (pg. 110, col. 3)(limitations of Claim 30). A four STR system, HUMCD4, HUMHPRT, HUMTH01, HumARA, was explored using additional amplification cycles.

Fregeau describes multiplex amplification of polymorphic STR sequences of loci including HUMHPRTB, HUMTH01, HUMCD4, HUMFABP and HUMPLA2A (pg. 117, col. 3, para. 2)(limitations of Claim 26). Empirical evaluation, a specific annealing temperature for each of the STR systems was found to generate consistent allelic profiles with high specificity and sensitivity after 28 cycles of amplification (pg. 115, col. 1). Several benefits of STRs analysis was elucidated including minimal only amounts of template DNA need to be used, the STR alleles can be resolved on sequencing gels using radiolabeled primers or having been processed with cold primers and detected after silver staining, and STRs are amenable to automation (pg. 100-101)(limitations of Claim 30). Further, Fregeau teaches that careful selection of a refined polyacrylamide gel system and appropriate STR loci that have allele size ranges that are mutually resolvable should allow for additional systems to be analyzed with the same fluorescent tag (pg. 117, col. 3).

Kimpton describes the multiplex amplification of polymorphic STR sequences of loci including HUMVWA31, HUMTH01, HUMF13A1, HUMFESFPS, HUMCD4, HUMDHER, HUMCYARO3, HUMAPOAII, HUMPLA2A, HUMIIDA, HUMFABP, HUMGABGA, HUMACTBP2 and D21S11. In Kimpton the combinations of loci are not identical to the combinations claimed. However, Kimpton performs multiplex amplification of STR containing loci in combinations of two, three, four, and seven, chosen loci from HUMVWA31, HUMTH01, HUMF13A1, HUMFESFPS, HUMCD4, HUMDHER, HUMCYARO3, HUMAPOAII, HUMPLA2A, HUMIIDA, HUMFABP, HUMGABGA, HUMACTBP2 and D21S11. Kimpton teaches primers for the amplification

of HUMACTBP2, HMAPOAII, HUMFABP, HUMTH01, HUMvWA31/A which are identical to the primers taught in the instant application, namely SEQ ID NO: 1, 4, 15, 27, and 32. Kimpton teaches the PCR component concentrations and cycling parameters were optimized for each loci individually. The STRs suitable for co-amplification (multiplexing) were then selected on the basis of similar optimal reaction conditions and compatible allele size ranges (pg. 16, col. 1). Efficient amplification of all loci in multiplex systems was achieved by the adjustment of annealing temperature and individual primer concentration (pg. 19, col. 3). Further, STR loci with overlapping allele size ranges were differentiated by use of different fluorescent dye labels (pg. 16, col. 1).

Urquhart teaches a method of simultaneously determining the alleles present in at least two STR loci. Urquhart teaches a method of preparing DNA from whole blood and performing a PCR amplification using genomic DNA. Each of two primers for each locus were added to the mixture and PCR was performed. The PCR products were electrophoresed in agarose gels, purified and sequenced (pg. 14, col. 1-2)(limitations of Claim 21-22, 26, 48, 50-51). Urquhart teaches primers which are identical to SEQ ID NO: 10, 15, 27, and 32 (Table 1)(limitations of Claim 27). Urquhart also teaches primers which are very homologous to SEQ ID NO: 11, 16, 25, 26 and 31. The alleles were evaluated by separating sizing alleles with an allelic ladder (pg. 14, col. 1)(limitations of Claim 28). Further, Urquhart teaches markers used in the quadruplex STR system were labeled fluorescently (pg. 13-14). The DNA obtained was prepared from blood (pg. 14, col. 1)(limitations of Claim 33). The conditions for the reaction were optimized in respect to the different STR's incorporated into the reaction (pg. 14, col. 2).

The primers used in the study were all derived from the published or GenBank sequences (pg. 14, col. 1). Although Urquhart does not specifically teach **all** of the recited combinations disclosed in the instant application, Urquhart, does teach the amplification of HUMVWFA31, HUMTH01, HUMF13A01, HUMFES/FPS, HUMCD4, HUMPLA2A1, HUMFOLP23, HUMCYAR04, HUMTFIIDA, HUMFABP, HUMGABRB15, and HUMD21S11 (pg. 14, col. 2). Urquhart teaches that the annealing temperature for HUMTH01, HUMCD4, HUMPLA2A1, HUMFOLP23, HUMCYAR04, HUMTFIIDA, HUMFAB, HUMGABRB15 and HUMD21S11 are all 60 degrees (pg. 14, col. 2).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to have modified the teachings of Caskey and Kimpton (Int. J. Leg. Med) with the loci of Fregeau, Kimpton or Urquhart to obtain the claimed invention based on the teachings of Caskey and Kimpton (Int. J. Leg. Med) in view of Fregeau, Kimpton or Urquhart because the skilled artisan would have been motivated by the teachings of Fregeau, Kimpton, or Urquhart to choose any reasonable number of known STR containing loci, and use them in desired combinations for detection and analysis of polymorphisms in STR loc. Further, it would have been obvious to have chosen any number of known STR containing loci which can be co-amplified together including those suggested by Fregeau and use them in desired combinations for detection and analysis of polymorphisms in STR loci, because such a co-amplification was in fact performed by Kimpton, Fregeau and Urquhart. Both Kimpton (Int. J. Leg. Med), Fregeau, Kimpton and Urquhart teach intricate details of multiplex PCR reactions, such as critical parameters for primer design, optimization of

cycling conditions, and pros and cons of gel electrophoresis, and visualization techniques (silver stain vs. fluorescence). Both Kimpton and Fregeau references comment on the empirical nature of selecting primers and amplification conditions to achieve an appropriate multiplex amplification system. Kimpton teaches "STRs suitable for co-amplification were selected on the basis of similar optimal reaction conditions and compatible allele size ranges" (pg. 16, col. 1, para 3). For example, Fregeau teaches, HUMTH01 and HUMCD4 both have annealing temperatures of 68 degrees, and have different allele size (bp) which do not overlap (Table 1 and Table 3). Similarly, ACTBP2 and HUMFABP both have annealing temperatures of 64 degrees and do not have overlapping allele sizes (Table 1 and Table 3). Therefore the at least two STR loci would contain clearly distinguishable STR allelic profiles (pg. 115, col. 3) and would have been obvious to combine the two STR loci to obtain the claimed invention. The choice of STR loci chosen to multiplex is dependent on what information is desired from the allele analysis. As exemplified in the art, gel analysis of several STR loci on the same gel saved time and reagents. One of ordinary skill in the art would have been motivated to design appropriate primers and optimize PCR conditions in order to co-amplify additional combinations of STR loci for the benefit of saving time, reagents and other supplies in the amplification process as taught by Fregeau (pg. 117). It is also evident from these references that the loci were chosen for their already demonstrated polymorphic properties and that implementation of multiplex amplification of combinations thereof was easily achieved by routine optimization of the well known PCR methodology adapted for multiplex purposes. As admitted in the specification,

"successful combinations are generated by trial and error (routine experimentation) of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified"(pg. 10, lines 10-13). Thus, the claimed invention would have been obvious over Caskey and Kimpton (Int. J. Leg. Med) in view of Fregeau, Kimpton or Urquhart.

2. Claims 21-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caskey (5,364,759) in view of GenBank STR lociHUMTH01, HUMTPOX, HUMF13A01, HUMFABP, HUMMYPOK, HUMBFXIII, HUMHPRTB, HSAC04, HUMCYP19 and HUMPLA2A1.

Caskey discloses the claimed method that includes obtaining a DNA sample, amplifying STR sequences from the DNA sample, and evaluating the amplification products for identification (col. 7, lines 4-10). Caskey describes a preferred Caskey discloses the claimed method that includes obtaining a DNA sample, amplifying STR sequences from the DNA sample, and evaluating the amplification products for identification (col. 7, lines 4-10). Caskey teaches a definition of "multiplex polymerase chain reaction (mPCR)"(col. 6, lines 34-68). Further, Caskey teaches that mPCR includes a) primers composed of similar GC base compositions and lengths, b) longer extensions times up to 8 fold the normally utilized times and c) minimization of the number of PCR cycles performed to achieve detection. Caskey teaches that mPCR reaction is optimized for each reaction (col. 6, lines 65-66). Caskey identifies STR loci by searching all human sequences in GenBank (Example 1, col. 8). Strategies to

determine the sequences flanking STRs are disclosed in Example 3 (col. 10). Although Caskey teaches that in a reaction with HUMARA and HUMFABP alleles appear as widely spaced doublets such that adjacent alleles overlap, different label may be applied to the different loci to unambiguously identify the alleles (col. 18). Caskey teaches the primers of SEQ ID NO: 15, 16, 19, 20, 27, and 28 as primers for the amplification of HUMFABP, HUMPRTB, and HUMTH01, respectively. As described in Example 7, the comparison of amplified alleles by polyacrylamide gel electrophoresis and visualization of the DNA by fluorescent analysis. STR markers can be detected with non-denaturing and denaturing electrophoretic systems (limitations of Claim 29). Silver staining detection methods are all applicable (limitations of Claim 30). Additionally, the loci are selected so that the amplification products of the alleles from different loci do not over lap (limitations of Claim 32). Further, Caskey teaches that the source of DNA to be tested can be any medial or forensic sample and can include blood, semen, vaginal swabs, tissue, hair, saliva, urine and mixtures of body fluids (col. 6, para. 2)(limitations of Claim 33). Caskey discloses the use of allelic ladders as internal standards (col. 7, lines 15-19, and col. 19, lines 15-18)(limitations of Claim 28). Additionally, Caskey teaches kits which contains a container having oligonucleotide primer pair for amplifying STRs and optionally, standards (col. 8 and col. 21, Example 10)(limitations of Claim 34-39, 55).

Caskey does not specifically teach the recited locus combinations.

However, the STR loci HUMTH01, HUMTPOX, HUMF13A01, HUMFABP, HUMMYPOK, HUMBFXIII, HUMHPRTB, HSAC04, HUMCYP19 and HUMPLA2A1 have

been taught by GenBank Accession No: HSAC04, M28420, M21986 J03834, M64554 J05294, M18079 J03465, M26434, M87312, M22970 M14965, D00269, M68651, and M25858 M25716.

Furthermore, rather than citing STR containing loci, Caskey refers to STR sequences by their alphabetical designation as indicated in Table I. Additionally, Caskey does not recite locus combinations in examples 4-7 and tables 6-9, where data from multiplex amplification of said alleles is performed and analyzed. Caskey describes the level of skill of an ordinary artisan by stating that once STR sequences and their flanking sequences are obtained, primer pairs may be designed and synthesized according to the flanking sequences and PCR amplification and comparison of amplified products may be performed to detect the short tandem repeats (col. 4, lines 9-17, col. 5, lines 16-53, col. 6, lines 58-60). Identical primers were used in the instant application for HUMFABP, HUMTH01, and HUMPRTB, therefore, the method by which Caskey derives primers for STR loci appears to be consistent with the method of the instant application. Caskey also comments on the empirical nature of multiplex amplification reactions and points out that each reaction must be optimized (col. 6, line 65).

Therefore, to one of ordinary skill in the art at the time the invention was made, it would have been **prima facie** obvious to use any number of primers, including SEQ ID NO: 1-32, among other possible sequences that could accomplish the same goal for the process of simultaneously amplifying specified loci which provide a different pattern and thus a means of confirmation or subsequent analysis. SEQ ID NO:s 1-14, 17-18, 21-26,

29-32 are not specifically taught by Caskey as specific primers for the respective STR loci. The claimed primers, however, would have been obvious based on the teaching of Caskey about primer design and synthesis and the known sequences of the claimed loci, which were available from GenBank. Additionally, Caskey was able to perform multiplex amplification of HUMTH01 in combination with other loci, which reiterates the level of skill in the art. As admitted in the specification, "successful combinations are generated by trial and error (routine experimentation) of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified"(pg. 10, lines 10-13). Therefore, the claimed invention would have been obvious over Caskey in view of the GenBank entries.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 21, 26-31, 33-34, 39, 48-51, 53-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

claims 1-4 of U.S. Patent No. 5,783,406. An obvious –type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 21, 48 are generic to all that is recited in claim 1 of U.S. Patent No. 5,783,406. Specifically, the method of the patent requires detecting HUMCSF1PO, HUMFESFPS and HUMTH01. For example, the instant claims are drawn to methods of simultaneously determining at least two makers selected from HUMCSF1PO and HUMTH01. Therefore, the claimed methods fall within the scope of the claims already patented.

With respect to Claims 27, 50, 51 the instant claims are drawn to methods requiring primer pairs for amplification of at least one loci. The method of Claim 27 of the instant specification differs from Claim 1 of 5,783,406 in that it fails to disclose the specific sequences of the primers for the locus-specific primers. However, the teachings of 5,783,406 provides numerous primers which allow amplification in multiplex systems. For example the primers for the loci HUMTH01 of 5,783,406, namely SEQ ID NO: 21 and 22, are identical to SEQ ID NO: 27 and 28 of the instant application. Therefore, it would have been obvious to modify the method of Claim 1 of U.S. Patent No. 5,783,406 such that the specific locus-specific primers were employed.

One having ordinary skill in the art would have been motivated to use the specific primer pairs taught within the supporting portions of 5,783,406.

With respect to Claims 28-31, 53-54 of the instant application, the specification of 5,783,406 specifically teaches and describes the method of separation and detection of the multiple alleles using separation by denaturing polyacrylamide gel electrophoresis and comparison to alleleic ladder using silver staining or fluorescence detection (col 9; col 11-12). Therefore, it would have been obvious to modify the method of Claim 1 of U.S. Patent No. 5,783,406 such that the alleles were separated by denaturing polyacrylamide gel electrophoresis prior to the comparing step of the patent which compares the co-amplified sequence to allelic ladders. One having ordinary skill in the art would have been motivated to use the comparing methods taught within the supporting portions of 5,783,406.

Claim 33 of the instant application is directed to a DNA sample which may be blood. Claim 1 of 5,783,406 teaches using a DNA sample to be tested. The specification of 5,783,406 teaches extracting DNA from blood samples, hair, semen, placental cells, fetal cells (col 10). Therefore, the ordinary artisan would have been motivated to have used DNA samples which were successful as taught by the specification of 5,783,406.

With respect to Claims 34, 39, 55 of the instant application, Claims 3-4 of 5,783,406 are directed to kits comprising primers directed to HUMCSF1PO. The specification of 5,783,406 teaches kits that utilize the process described (col 12). Therefore, it would have been obvious to place primers for each of the loci being

examined in a container for carrying out the method in a rapid cost effective manner. One having ordinary skill in the art would have been motivated to have designed kits which comprise reagents for the method which were taught within the supporting portions of 5,783,406.

9. Claims 21, 26-31, 50-51, 53-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 of U.S. Patent No. 5,674,686. An obvious –type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 21, 48 are generic to all that is recited in claim 1 of U.S. Patent No. 5,674,686. Specifically, the method of the patent requires detecting HUMCSF1PO, HUMFESFPS and HUMTH01. For example, the instant claims are drawn to methods of simultaneously determining at least two makers selected from HUMCSF1PO and HUMTH01. Therefore, the claimed methods fall within the scope of the claims already patented.

With respect to Claims 27, 50, 51 the instant claims are drawn to methods requiring primer pairs for amplification of at least one loci. The method of Claim 27 of

the instant specification differs from Claim 1 of 5,674,686 in that it fails to disclose the specific sequences of the primers for the locus-specific primers. However, the teachings of 5,674,686 provides numerous primers which allow amplification in multiplex systems. For example the primers for the loci HUMTH01 of 5,674,686, namely SEQ ID NO: 21 and 22, are identical to SEQ ID NO: 27 and 28 of the instant application. Therefore, it would have been obvious to modify the method of Claim 1 of U.S. Patent No. 5,674,686such that the specific locus-specific primers were employed. One having ordinary skill in the art would have been motivated to use the specific primer pairs taught within the supporting portions of 5,674,686.

With respect to Claims 28-31, 53-54 of the instant application, the specification of 5,674,686 specifically teaches and describes the method of separation and detection of the multiple alleles using separation by denaturing polyacrylamide gel electrophoresis and comparison to alleleic ladder using silver staining or fluorescence detection (col 9; col 11-12). Therefore, it would have been obvious to modify the method of Claim 1 of U.S. Patent No. 5,674,686 such that the alleles were separated by denaturing polyacrylamide gel electrophoresis prior to the comparing step of the patent which compares the co-amplified sequence to allelic ladders. One having ordinary skill in the art would have been motivated to use the comparing methods taught within the supporting portions of 5,674,686.

Claim 33 of the instant application is directed to a DNA sample which may be blood. Claim 1 of 5,674,686 teaches using a DNA sample to be tested. The specification of 5,674,686 teaches extracting DNA from blood samples, hair, semen,

placental cells, fetal cells (col 10). Therefore, the ordinary artisan would have been motivated to have used DNA samples which were successful as taught by the specification of 5,674,686.

10. Claims 21-22, 26-34, 39, 48-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 6,221,598. An obvious –type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 21, 48 are generic to all that is recited in claim 1 of U.S. Patent No. 6,221,598. Specifically, the method of the patent in one embodiment is directed to detecting HUMPOX, HUMCD4 and HUMTH01. For example, the instant claims are drawn to methods of simultaneously determining at least two makers selected from HUMCD4 and HUMTH01. Therefore, the claimed methods fall within the scope of the claims already patented. The method of Claim 22 in the instant application and the method of Claim 1 of 6,221,598 encompass the same scope. Specifically, the first set of short tandem repeats is the same as those listed in Claim 1 of 6,221,598.

11. Claims 21-34, 36-37, 39-41, 44, 46-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 5843660. An obvious –type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 21, 48 are generic to all that is recited in claim 1 of U.S. Patent No. 6,221,598. Specifically, the method of the patent in one embodiment is directed to detecting HUMCSF1PO, HUMPOX, HUMCD4 and HUMTH01 (limitations of Claim 24) or HUMCSF1PO, HUMPOX, HUMF13A01 and HUMTH01 (limitations of Claim 25). For example, the instant claims are drawn to methods of simultaneously determining at least two makers selected from HUMCD4 and HUMTH01 (limitations of Claim 21); HUMCSF1PO, HUMPOX, and HUMTH01 (limitations of Claim 22). Therefore, the claimed methods fall within the scope of the claims already patented. Claim 4 of the patent is directed to determining a set of seven loci which comprises HUMTPOX, HUMTHO01 and HUMCSF1PO (limitations of Claim 23). Claim 34 of the instant application is drawn to a kit comprising primers for at least two loci which in one embodiment is directed to HUMCSF1PO and HUMTPOX. Claim 25 of 5,743,660 teaches a kit comprising primers from D16S539, D7S820, D13S317,

D5S808, HUMCSF1PO, HUMTPOX which encompasses Claim 34. Moreover, Claim 25 of 5,743,660 teaches a kit comprising primers from D16S539, D7S820, D13S317, D5S808, HUMCSF1PO, HUMTPOX, HUMTH01 and HUMvWFA31 which encompasses Claim 36-37 of the instant application. Claim 4 of 5,743,660 teaches a method using D16S539, D7S820, D13S317, D5S818, HUMCSF1PO, HUMTPOX and HUMTH01 (limitations of Claim 40, 41).

12. Claim 1-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 9-18, 21-23, 60-36, 39 of copending Application No. 09/199,542. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are drawn to detecting two or more STR loci. The claims of the allowed application are directed to detection of thirteen STR loci. The set of 13 STR loci encompasses the set of 2 loci of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. It is noted that the claims for 09/199,542 have been allowed but have not matured into a patent. Therefore, upon publication of the patent, this rejection will no longer be considered provisional.

Conclusion

13. No claims allowable.

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14. Any inquiry concerning this communication or earlier communications from t examiner should be directed to examiner Jeanine Goldberg whose telephone numb (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examine supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
July 1, 2002

W. Gary Jones
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Technology Center 1600